- Under battlefield conditions, the M291 skin decontamination kit, not Cetaphil® cleanser and water, would be used to decontaminate skin after exposure to permeants. It is unclear whether results obtained following decontamination with Cetaphil® and water can be extrapolated to circumstances in which the M291 skin decontamination kit is used.

Study Title: "The Protective Efficacy of the Topical Skin Protectant ("TSP") Against Methyl Nicotinate Under Sweating Conditions"

Study Dates: 12/22/98-04/09/99
Study Location: St. Petersburg, FL
[redacted] Study No.: 98-101117-72
Sponsor Protocol No. A-8522

Investigators: Principal Investigator: William Cunningham, M.D.
Associate Investigator: Loraine Harnisch, B. Sc. (responsible for accurate execution of the protocol)
Medical Monitor: Harold B.Seder, M.D. (responsible for ensuring subject's meet inclusion/exclusion criteria, for providing the medical examination)

Objective/Rationale:
The objectives of this Phase 2 clinical trial were (1) to perform dose ranging to determine the relationship between the dose of contact irritant methyl nicotinate (Mnic) and the degree of cutaneous vasodilation [Pilot Phase], and (2) to assess whether TSP protects the skin against the penetration of Mnic after exposure to the chemical under conditions of sweating [Main Phase].

Design
The study was a single center, randomized, unblinded investigation employing a complete block design (subjects enrolled in blocks of 5). Patients served as their own controls in the study. The study was conducted in two phases: pilot phase and main phase. Patients were enrolled either in the pilot phase or the main phase. Each phase had two periods: pre-conditioning period and test period. Screening occurred on Day -4. Testing occurred at Day 1. The last office visit was at Day 1.

Reviewer's Comment: Sponsor notes that "this study was not designed to be a blinded study as data was collected through primary instrumental evaluations" [Laser Doppler Velocimetry (LDV), which is capable of measuring mean blood flow without skin contact]. The sponsor notes that "the presence of the TSP test article was clearly visible...therefore, it was neither feasible nor necessary to blind...the evaluator." (Vol 2.39. pg. 28). Of note, in medical officer's review of the draft protocol [IND [redacted] 031], the medical officer stated that the protocol "has reasonably adequate safeguards to ensure blinding, so long as the investigator(s) responsible for measuring erythema are different individual(s) than those investigator(s) responsible for applying TSP, Mnic or vehicle to the volar forearms of volunteer subjects." It would have been feasible, and

practical, for the technician interpreting the LDV readings to be blinded with respect to whether Mnic or water had been applied to test sites. While instruments are objective, the humans who use them are not necessarily objective. As one potential source of bias, during laser doppler readings, it is necessary for all the patient's test sites to be equidistant from the laser source. Sites further from the laser would be read as having lower flux, and sites closer to the laser would give readings of higher flux. Theoretically, inadvertent misalignment of the laser could generate anomalous recordings.

PROTOCOL OVERVIEW:
Population, procedures
Subjects qualified for the study during the screening visit (Day –4).

For the pilot phase, 28 subjects were enrolled and 22 subjects completed the study. Five of the subjects in the pilot phase failed to complete "due to schedule conflicts", while one failed to complete due to "personal reasons" [not otherwise specified] (Vol. 2.39, pg. 42).

For the main phase, 42 subjects were enrolled, 37 of whom completed the Main Phase and 33 of whom were categorized as 'responders' to Mnic. The data from these 33 'responders' were used by sponsor to analyze the efficacy of the TSP. The reasons why five subjects failed to complete the Main Phase were because of an allergic reaction to latex adhesives (one patient), schedule conflicts (three patients), and non-compliance (caffeine ingestion) (one patient).

Reviewer's Comment:
The individuals classified as "non-responders" by Sponsor developed erythematous changes in their skin at the unprotected sites where methyl nicotinate was applied. Thus, the justification for classifying them as non-responders seems strained. Accordingly, all 37 individuals from whom Laser Doppler Velocimetry readings were collected constituted the evaluable population for Agency analysis.

INCLUSION CRITERIA
- Subjects were male and female, unrestricted as to race or ethnicity, between 18 – 55 years of age, and in good general health as established through a medical examination.
- Subjects were HIV negative as determined by interview during medical examination, review of medical history and blood test.
- Subjects had a blood pressure (either systolic or diastolic) no greater than 150 / 90, a pulse rate between 60 and 100 bpm, and a body temperature no greater than one degree above normal the day of the investigation (as determined by a brief medical screening conducted by a trained clinical technician prior to admission to the "hot room").
- Female subjects were surgically sterile, post menopausal, or using an acceptable method of birth control and had a negative urine pregnancy test at enrollment.
- Subjects were willing to abide by the rules of the study.

- Subjects' volar forearms were free of any scars, tattoos, cuts or abrasions. In addition, the subjects did not have significant body hair on the volar forearm which would interfere with the instrumental evaluation.
- Subjects were willing and able to read and sign the informed consent statement and photographic release form.
- Subjects were willing and able to refrain from caffeine and nicotine intake 12 hours prior to the start of and throughout the duration of the test period of the investigation.
- Subjects were willing and able to refrain from the use of any medication(s), Rx or OTC, during the 7 days immediately proceeding the test period of the investigation. The restricted medications are those classified as antihistamines, anti-inflammatory agents including NSAIDs, corticosteroids, cortisone containing preparations, aspirin, non-steroidal anti-inflammatories, nicotine or other transdermal delivery patches, diet pills or other medications which may, in the opinion of the investigator, interfere with any of the evaluations.

EXCLUSION CRITERIA

- Female subjects were not pregnant or breast feeding.
- Subjects did not have a skin disorder or condition(s) that would interfere with the study evaluation (i.e., eczema, psoriasis, atopic dermatitis, sunburn or significant tanning, etc.).
- Subjects did not have a history of chronic or systemic disease including rheumatoid arthritis or other inflammatory disorders, diabetes, high blood pressure, history of epilepsy, severe asthma, etc.
- Subjects were not using any medication (Rx or OTC) on a regular basis such as antihistamines, insulin, anti-inflammatory agents, including NSAIDs, corticosteroids, cortisone containing preparations, aspirin, nicotine or other transdermal delivery patches, diet pills, or other medications which may, in the opinion of the Investigator, interfere with any of the evaluations.
- Subjects did not have a known allergy or sensitivity to any components of the test materials, adhesive materials, latex, or any of the medications previously listed.
- Subjects were not moderate or heavy smokers (>10 cigarettes per day as determined by interview) who would be unlikely to successfully refrain from smoking 12 hours prior to and throughout the duration of the test period of the investigation.
- Subjects were not moderate or heavy consumers of alcohol (alcohol consumption occurring > twice weekly or >4 alcoholic beverages regularly consumed per week as determined by interview) who would be unlikely to successfully refrain from alcohol consumption 24 hours prior to and throughout the duration of the test period of the investigation.

Protocol Synopsis

The clinical protocol for both the pilot phase and the main phase calls for two study visits: screening (Day –4) and testing (Day 1). The following table depicts the events that were supposed to occur on these two visits.

PERIOD	EVENT	DAY –4	DAY 1
Screening Visit.	Obtain Informed Consent Statement from Volunteer	X	
Screening Visit.	Medical Examination of Volunteer by Medical Monitor, including HIV blood draw	X	
Screening Visit.	Interview and completion of Required Investigation Documentation	X	
Screening Visit.	Schedule Test Appointment	X	
Screening Visit.	Notification and Exclusion of Volunteers with positive HIV test results	X	
Test	Medical Screening: Vital Signs by Medical Monitor or Designee for final qualification		X
Test	Volunteer Acclimates in Controlled Environment to Ambient Conditions (30 Min)		X
Test	Application of the TSP after 30 min. acclimation & baseline evaluations		X
Test	Challenge with Mnic and Placebo 60 minutes after TSP application, followed by 80 min. thermal stress (EnvCh)		X
Test	Sweat Gland Activity established (Baseline, 20, 40, 60 and 80 min. post-thermal stress)		X
Test	*Visual Evaluation (Baseline, 0, 2.5, 5.0, 10, 15, 30, 45, 60 and 80 min. post Mnic app; Time to onset of response documented; main timing adjusted based on pilot results)		X
Test	*Scanning LDV Evaluation (Baseline, post-Mnic; initial timing based on pilot visuals)		X
Test	*Clinical Photography (Baseline, post-Mnic; timing based on pilot eval. Of mean onset)		X
Test	*Colorimetric Evaluation (Baseline, post-Mnic; timing base on pilot visuals)		X
Test	TEWL Evaluation (Baseline, following completion of post-Mnic evals.)		X
Test	Sebumetric Evaluation (Baseline, following completion of post-Mnic evals.)		X
Test	Post-Treatment Cleansing of Test Sites after completion of all evaluations		X
Both	Adverse Events		X

*indicates evaluation of reactivity to Mnic

Table 13.0a, Vol. 2.39, page 101.

Screening:
The activities appropriate for screening (see above table) are performed. In addition, subjects are reminded that they are not to smoke cigarettes or consume caffeine containing foods and beverages for 12 hours before the scheduled Test Period and during the Test Period, or to consume alcoholic beverages 24 hours before the Test Period and during the Test Period.

Preparation:
A 6 cm X 20 cm rectangular area was marked on the volar aspect of each forearm by the technician. Within each rectangle, 3 circular test regions 27 mm in diameter, each of whose centers are separated by approximately 2.5 cm, was marked by the technician. Subjects entered an ambient conditioning room (65-70°F, 30-50% relative humidity) for 30 minutes.

Pilot Phase of Study:
Overview:
The purposes of the pilot study were to optimize the scanning laser doppler instrumental parameters and to identify the appropriate methyl nicotinate dose, solution concentration, and delivery volume that would provide a measurable erythema on untreated, unprotected skin but would not break through the TSP protective barrier.

Reviewer's Comment: This conceptual approach is satisfactory if the purpose of the study is to test the hypothesis that TSP has no effect upon penetration of methyl nicotinate after sweating has occurred. However, it is unclear how the degree of protection observed under these optimal conditions could be extrapolated to other challenge conditions that try the protective efficacy of TSP more vigorously.

Protocol Synopsis (as detailed in Pilot Study Summary):
A brief discussion of the technique of Laser Doppler Velocimetry (LDV) is necessary for an understanding of how the TSP barrier property was assessed in this study. LDV is a technique that determines changes in the product of number and velocity of red blood cells moving through the skin circulation under observation. It is the change in this product that accounts for the change in visible erythema. A beam of laser light is directed through an optical fiber onto the skin surface of interest. Light enters the skin and is reflected both from nonmoving tissues and from mobile red blood cells. The former reflects radiation at the incident frequency, but the frequency of light backscattered from moving erythrocytes is shifted in proportion to their velocity (the Doppler effect). The returning signals are guided from the tissue surface through a second optical fiber onto a photodetector, which then can quantitate the Doppler shift of the signal (which is proportional to microcirculatory flow). Laser Doppler Image processing software can be used to define a region of interest (i.e., a circular site on the ventral forearm), which contains a set of pixels. Each pixel has its own flux value calculated from the Doppler shift of the reflected light. Mean flux within the region of interest, which is the average flux from all included pixels, is then calculated.

Subjects were positioned on the scanning laser doppler imaging positioning device and had test sites marked on both arms. Seated in an armchair with feet elevated, subjects began a 30 minute equilibration period under ambient conditions. 50 microliters of TSP paste was applied with a positive displacement microdispenser to the appropriate test sites, which was then distributed across the site with a saturated latex finger cot and smoothed with a spoon-tipped spatula to form a uniform, thin, uninterrupted film approximately 0.1 mm in thickness. Subjects completed a 60 minute post-TSP application equilibration period under ambient conditions.

After this equilibration period, a scanning laser doppler image of the regions of interest on the ventral forearms was obtained. Subjects then entered a room (temperature of 100 °F, relative humidity of 30<%RH<40) for an 80 minute period of thermal stress. A droplet of Mnic in deionized water solution, dispensed by a microdispenser, was applied to the area, then wicked away with a cotton tipped applicator two minutes later. While in the hot room, visual inspections of the regions of interest occurred at 2, 4, 6, 8 and 10 minutes after Mnic application. Subjects were then escorted from the hot room and seat next to the scanning laser doppler imaging station where each arm was gently patted one time with a double layer of ——— tissue. A second scanning laser doppler image was collected, clinical photography was performed, and test articles/residual challenge was washed from the subjects' arms with the assistance of clinical personnel, using Cetaphil® liquid cleanser and lukewarm tap water. Skin was patted dry.
The conduct of the pilot phase of this study, as described in the "Pilot Study Summary",Vol. 2.41, page 186, appears not to have scrupulously followed the original clinical protocol as planned in Vol. 2.39. Three sets of measurements (colorimetric evaluation, TEWL evaluation, and sebumetric evaluation) were not collected in the Pilot Study Summary, though they were part of the original clinical protocol.

In a BZ submission dated October 18, 1999, sent in response to an information request dated October 12, 1999 from Agency, Sponsor informed Agency that colorimetric readings were suspended after the first five subjects in the pilot phase were examined in this manner. The reasons provided for this suspension was that "there are technical barriers in the present experimental design that limit this technique. Increased redness of the skin due to thermal stress reduces the effective dynamic range of measurements from baseline to methyl nicotinate challenged test sites. However, an even greater technical barrier is the loss of ability to obtain an accurate chromametric measurement at test sites to which TSP has been applied." (pg. 13 of 24, Vol. 4.1, Enclosure 2).

TEWL was also not measured after the first five subjects because the sponsor decided that "although knowing the integrity of the barrier to passage of water vapor from the skin's surface might be indicative of barrier efficacy, knowledge of its antipenetrant activity to an external agent is much more critical. Concomitant testing has shown that changes in data provided by LDV scans and visual scores...provide a reliable and sensitive means of evaluating TSP efficacy." In response to Agency information request, sponsor submitted in a BZ submission dated 10/27 the TEWL measurements for the five subjects in which the data were collected. In three of those subjects, TEWL measurements were obtained at baseline and after exposure to the test environment.

There was no significant increase in TEWL levels after exposure in the test environment, suggesting that TSP barrier was not compromised, but drawing conclusions from such a small set of observations is problematic.

Regarding sebumetry measurements, Sponsor noted in the October 18 response that "it was found that the amount of TSP that is placed at each TSP-treated test site does not allow an accurate and reproducible measurement [of skin surface residue] to be made. Therefore, this method was not considered further for use in the main phase of this study."

Reviewer's Comment:
These changes in the clinical study design, which were not reviewed by Agency before they were implemented, do not seem to have impacted upon either patient safety or study design bias. Data from more TEWL evaluations might have provided more information about the durability of the TSP barrier after subjects' prolonged exposure under sweating conditions because transepidermal water loss is a surrogate marker for barrier integrity, and if the TSP barrier can withstand sweating, then one would expect TEWL to be the same before and after incubation under sweating conditions.

Results:
LDV measurements were not performed on the other 12 subjects (Subjects 001-012) in the pilot study. In response to an Agency Information Request dated October 12, 1999, Sponsor submitted the LDV measurements from the permeant-ranging and time-ranging components of the pilot study. Based on the few subjects (13-16, 22,23) in which comparisons are possible, it appears that the magnitude of the TSP-mediated reduction in vasodilation is approximately the same at 10 minutes and 20 minutes after challenge. Sponsor utilized the pilot phase data to:

- **Optimize settings for the Laser Doppler Imager.** The sponsor reports that a 4 millisecond/pixel scan speed with a 256 X 256 scan resolution for the field of scan at a distance of 40 cm from the scanned surface is necessary to detect the relatively small Mnic induced vasodilatation above that of the background thermal vasodilatation which occurs under sweating conditions. A scan under these conditions takes 7 minutes 48 seconds.
- **Optimize Mnic concentration for demonstrating TSP protection at 2.5 mM.** Subjects 015, 014, 016, and 013 were challenged with 10 mM Mnic; these four subjects plus Subjects 023, 022, 018, and 025 were challenged with 5 mM Mnic. According to the sponsor, "Mnic solutions at 5 mm and above provided good, visible and measurable reaction on both untreated, unprotected skin and TSP protected skin...the 5 mm solution provides a clean response but reflects significant minimization of exposure to the challenge agent, not virtual prevention from exposure."
- **TSP Artifact, and its Circumvention.** Measurement of flux on TSP-treated skin is complicated by "shine" artifact induced by reflection of laser light from the TSP that is unrelated to underlying Mnic-induced flux. This artifact is more noticeable on

darkly pigmented and on-non-xerotic skin. This artifact can be circumvented by gently patting the treated sites with Kleenex prior to flux measurement.

- **Optimal Mnic droplet size for demonstrating TSP protection is 7.5 microliters.** According to the sponsor, droplets larger than this size may not maintain their shape integrity or may travel across the test site while a subject is actively perspiring. The dispersion of large droplets that results under these conditions reduces the consistency in the dose response behavior. It also induces a measurable erythematous response under sweating conditions that is detectible above the thermal vasodilatation induced under sweating conditions.

Reviewer's Comment: It is unclear whether TSP efficacy can be generalized to conditions in which challenge droplets are greater than 7.5 microliters in size.

Main Phase:

Baseline Evaluation:

After thirty minutes at the ambient conditions, the following baseline evaluations were performed: visual inspection, scan of cutaneous blood flow (using a Laser Doppler Imager), clinical photography, and sweat gland activity (using silicone impression technology).

VISUAL INSPECTION SCORES	
Score	**Description**
0	No reaction; no erythema
1	Mild reaction; minimal macular erythema, faint but definitely pink usually covering the entire test site
2	Moderate reaction; moderate macular erythema, definite redness, possible edema
3	Strong to severe reaction; intense redness, probable edema, possible spreading

Intermediate scores of 0.5, 1.5, and 2.5 are permitted.

TSP Application:

Randomization of the TSP versus untreated skin sites with respect to right and left forearms was done so that for each subject, all test sites on one arm were treated with TSP and test sites on the other arm remained untreated. Site pairs were chosen on the TSP-treated and untreated forearms in accordance with randomization to receive the MNic challenge, a vehicle challenge, or no challenge, but challenge was not to occur until after exposure to the hot, humid environment.

A fixed volume, positive-displacement micro-dispenser was used to deliver 50 microliter of TSP to the center of each designated test site to deliver a dose of approximately 11 microliter of TSP per cm^2 skin area. The TSP was then distributed across each test site using a small, spoon-tipped, stainless steel spatula to form a thin, uniform film

approximately 0.1 mm in thickness. The Associate Investigator or trained study technicians applied the TSP.

Reviewer's Comment: It is unclear whether efficacy results obtained under such artificial conditions (dispensing with a micro-dispenser, followed by spreading with a spatula of the dispensed TSP) can be generalized to the expected method of application by soldiers (i.e. spreading with fingertips).

Setting/Drying of TSP on the Skin:
Subjects were required to remain in the ambient conditioning room for an additional 60 minutes following application to mimic "wear time" of TSP previously employed in other investigations.

Reviewer's Comment: The purpose of the 60 minute "wear time" is unclear. Given the intended use of TSP, it seems plausible that battlefield personnel may not always have the luxury of an hour's notice of impending chemical attack before they have the opportunity to apply the TSP. Hence, it is incumbent upon the sponsor to test TSP efficacy under more realistic conditions (i.e., immediately after TSP application. Since TSP is a viscous suspension that does not contain volatile solvents that would be expected to evaporate following contact with human skin for one hour. Hence, no expected change in the physico-chemical characteristics of the TSP would be expected following prolonged exposure to skin.

Heat and Mnic Challenge:
Volunteers entered the challenge environment (temperature 100 °F; percent relative humidity 30<%RH<40), and remained for 80 minutes. Sweat gland activity at a control site was documented at 20, 40, 60 and 80 minutes after entrance into the challenge environment, using silicone replicas. Volunteers then undergo another visual evaluation.

A site pair was defined as two sites, one on each arm, that had the same relative location (i.e., proximal, medial, or distal to the elbow). Site pairs that received Mnic challenges were randomly selected between the proximal (sites 1 and 4) and distal (sites 3 and 6) sites. Site pairs receiving vehicle challenge or no challenge were then randomly selected from the remaining sites over proximal, middle (sites 2 and 5), or distal site locations. Both sites within a given site pair always received the same challenge (i.e., if the proximal location on the right volar forearm received TSP and Mnic challenge, then the proximal location on the left volar forearm received no TSP and Mnic challenge.

After 80 minutes, the three test sites on each forearm received either Mnic (7.5 microliters of 2.5 mM methyl nicotinate dispensed with a microdispenser), or distilled water, or no challenge. Two minutes after application, droplets were wicked away using a cotton swab applicator.
The six test skin sites were examined by a trained evaluator at the moment of wicking of the challenges and at 2, 4, 6, and 8 minutes after wicking.

Reviewer's Comment: It is unclear whether efficacy results observed under conditions where a model permeant is exposed to TSP for only 2 minutes can be extrapolated to conditions in which exposure is longer than 2 minutes.

Post-challenge Monitoring:
Volunteers leave the hot room. To prevent the appearance of shine artifacts resulting from reflection of the laser beam off the TSP film that would otherwise appear during the LDV scan, the test sites on each arm are gently patted with a double layer of [redacted] tissue., Collection of Laser Doppler Velocimetry data was initiated approximately 11 minutes after wicking and required about 7 minutes to complete.

Next, clinical photographs of the test sites were taken. The protocol specified that post-treatment chromametry, transepidermal water loss, and skin surface residue measurements are taken at each of the six skin test sites to assess the barrier integrity and substantivity of the TSP barrier following sweating and exposure to the challenge agent.

Reviewer's Comment: As was discussed in the section concerning the Pilot Phase of the study, no colorimetric evaluation, TEWL evaluation, or sebumetric evaluation were included in the study results of the Main Phase, though plans for these evaluations were part of the original clinical protocol.

TSP Removal
At 20 minutes after wicking, the TSP film was removed by the technician through careful scraping with a small, flat blade, stainless steel, dental spatula, and a second series of clinical photographs are taken to document any skin effects which may not have been visible due to the opacity of the TSP film.. Visual score was assessed by the technician, then subjects washed their skin with Cetaphil® liquid cleanser, lukewarm tap water, and patted their skin dry.

Primary Efficacy Variables:
The protocol did not unambiguously identify which method(s) were be used to evaluate TSP efficacy. Sponsor declares (in the Study Report) that the mean flux as measured by Laser Doppler Velocimetry collected from 11 to 18 minutes after wicking is the primary efficacy variable for this study.

Reviewer's Comment: The primary efficacy variable was not pre-specified in the Study Protocol. Based on which efficacy measures were collected in the main phase, only mean flux and visual scoring were possible candidates for the primary efficacy variable. The drawback with visual scoring was that it was unblinded, thus creating the possibility of observer bias. In addition, the presence of TSP residue might interfere with assessing the degree of erythema. Agency's analysis chose mean flux as the primary efficacy variable, with visual scoring as a secondary efficacy variable.

In addition to testing whether TSP retains any capacity to retard Mnic penetration after subject sweating, it would have been valuable for the Sponsor to test whether TSP blocks penetration rather than merely retarding it. To collect this information, instead of

measuring mean flux over one time period (from 11 minutes to 18 minutes after permeant application), measurement over multiple time periods would be needed. With the present study design, there is no information collected to address how much time beyond 11 to 18 minutes subjects have to decontaminate their skin under sweating conditions. The pilot phase data does suggest that TSP prevents vasodilation at longer time points, but as mentioned above, few serial LDV measurements were collected.

Clinical Endpoints:
Subjects' participation was complete after post-treatment cleansing of test sites had been performed.

Safety:
All adverse events temporally related to participation in the study were documented.

STATISTICAL ANALYSIS:
Sponsor's Analysis
For each arm, the mean flux scores for the three sites were ranked (3: highest, 1: lowest). Thus, if the TSP-treated-2.5 mM Mnic site ranks highest compared to the TSP-treated-0 mM Mnic or the TSP-treated-no treatment site for each study subject, then the TSP-treated-2.5 mM Mnic site has a mean rank score of 3.0. Two between-treatment analyses were conducted (among the three sites treated with TSP and among the three sites not treated with TSP) using the Friedman rank sum analysis. Fisher's LSD test was performed if significant differences ($p<.05$) were observed with the Friedman rank sum test. The following analyses were also performed:

- TSP-Treated versus TSP-Untreated by Type of Challenge
- Comparison of Types of Challenge (0.0 mM Mnic versus 2.5 mM Mnic versus "No Challenge") by TSP application (TSP-Treated and TSP-Untreated)

Reviewer's Comment:
The clinically relevant comparison for this study is the difference between the mean flux data of the 2.5 mM Mnic-exposed TSP-Treated versus 2.5 mM Mnic-exposed TSP-Untreated sites.

Demographics, Evaluability
Demographic and baseline characteristics for the 37 subjects in the main phase of the study are summarized in the following table.

Age (years)	
Mean (SD)	39.5 (9.00)
Range	(18, 53)
Gender	
Male	10 (27%)
Female	27 (73%)
Race	
Caucasian	34 (92%)
African American	1 (3%)
Asian American	2 (5%)
Source: Vol. 2.39, pg. 047	

Efficacy
Primary Efficacy Results

The following table compares the mean flux at the six sets of test sites for 33 "responder" subjects evaluated by the sponsor.

Comparison of Type of Challenge for TSP-Treated and TSP-Untreated Sites*		
Type of Challenge	TSP-Treated	TSP-Untreated
0.0 mM Mnic	114.01 +/- 7.51	127.68 +/- 6.66
2.5 mM Mnic	117.26 +/- 5.99	229.72 +/- 15.20
No Challenge	106.82 +/- 6.03	128.01 +/- 6.60
*Means +/- Standard Errors of Measurement are shown. Source: Vol. 2.39, page 053		

Under these experimental conditions, TSP abrogated Mnic-induced vasodilation.

Paired t-tests were used to compare the laser doppler velocimetry measurements of mean flux at Mnic-challenged, TSP-treated sites with the measurements of mean flux at Mnic-challenged, TSP-untreated sites within each subject. The null hypothesis, that TSP affords no protection from Mnic-induced vasodilation, predicts that the difference in mean flux measurements was zero. A positive value in the mean difference indicates that TSP protects against Mnic penetration. The following table depicts the results from paired t-tests performed on two sets of subjects: all 37 patients upon whom laser doppler velocimetry was performed, and the subset of 33 patients who were classified by sponsor as "responders".

Paired t-test Analyzing TSP-Treated vs. TSP-Untreated Test Sites				
Number of Patients	Mean Difference	Standard Error of Measurement	T statistic	P-value
37	101.23	11.86	8.54	<0.0001
33	112.46	11.82	9.52	<0.0001

For both populations analyzed, TSP protects significantly against Mnic-induced vasodilation.

As the following table shows, among the three challenged TSP-untreated sites, rank of mean flux was always highest at the 2.5 mM Mnic-challenged sites. Among the three challenged TSP-treated sites, the rank of mean flux trended higher at the 2.5 mM Mnic-challenged sites, but the rank was not uniformly above that of the other sites.

Comparison of Mean Rank by Type of Challenge, TSP-Treated and TSP-Untreated Sites		
Type of Challenge	Mean Rank, TSP-treated	Mean Rank, TSP-untreated
0.0 mM Mnic	2.09	1.55
2.5 mM Mnic	2.12	3.00
No Challenge	1.79	1.45
Source: Vol. 2.39, pg. 053	Friedman Rank Analysis p-value: 0.33; ANOVA p-value: 0.0001	

Secondary Efficacy Results

Visual erythema scores were zero for all sites at baseline, at one hour after TSP application (before entry into the test environment), and at T0 of challenge permeant application. The following tables depict the mean and standard error of measurement of the visual erythema scores for different types of challenge, for the TSP-untreated and TSP-treated sites.

Mean Visual Scores for TSP-Untreated Sites +/- STD							
Type of Challenge	T2	T4	T6	T8	T10	T22	T27
0.0 mM	0	0	0	0	0	0	0
2.5 mM	.03 +/- .17	.41 +/- .46	.80 +/- .38	.88 +/- .27	.92 +/- .25	.88 +/- .30	.82 +/- .33
No challenge	0	0	0	0	0	0	0
From Vol. 2.39, page 055							

Mean Visual Scores for TSP-Treated Sites +/- STD							
Type of Challenge	T2	T4	T6	T8	T10	T22	T27
0.0 mM	0	0	0	0	0	0	0
2.5 mM	0	.05 +/- .20	.13 +/- .27	.27 +/- .37	.33 +/- .40	.27 +/- .36	.20 +/- .33
No challenge	0	0	0	0	0	0	0
From Vol. 2.39, page 056							

Sponsor performed ANOVA to compare mean visual erythema scores of 2.5 mM Mnic challenged, TSP-treated versus TSP-untreated sites, and noted that the average scores for the TSP-treated group were always significantly lower than the TSP-untreated group.

Reviewer's Comment: Interpretation of visual erythema score analysis is complicated by the absence of blinding in the observers who scored erythema.

Safety

Extent of Exposure

Including pilot and main phases of the study, fifty nine subjects were exposed to TSP and challenge permeants in this study.

Discontinuations

No subjects were discontinued from the study due to laboratory abnormalities. According to sponsor, one subject (#38) failed to complete the study due to an allergic reaction to latex adhesives. Six subjects in the pilot phase, and four in the main phase, failed to complete the study due to personal reasons or non-compliance.

Reviewer's Comment: The reason for discontinuation of subject #038 is unclear. There is no place in the protocol where the subject would have been exposed to latex adhesives, and there is no indication that the subject was tested via patch testing for latex allergies, so the basis by which sponsor was able to determine that subject #038 experienced an allergy to latex adhesives is unclear. There is no information provided about whether this subject experienced an adverse effect associated with exposure to latex adhesive.

Adverse Events

There were no adverse events reported during the course of the study.

Laboratory Evaluations

There were no laboratory evaluations performed during the course of this study.

Reviewer's Comments/Conclusions of study results

This clinical study demonstrated that despite prolonged exposure to a hot, humid environment that induces perspiration through the TSP layer, TSP still reduces Mnic-induced vasodilation, at the dose of Mnic studied, for at least fifteen minutes after Mnic application. No treatment-emergent adverse events were associated with TSP use.

Because of the methodologic constraints of this type of study, the study does not resolve the following issues concerning TSP efficacy after subject exposure to a hot, humid environment:

- It is unclear how the degree of protection observed under these experimental conditions should be extrapolated to challenge with CWA/BWA:
  - It is unclear whether TSP efficacy can be generalized to conditions in which challenge droplets are greater than 7.5 microliters in size, or whether results following exposure to permeant for only 2 minutes can be extrapolated to conditions in which exposure is longer than 2 minutes.
  - It is unclear whether efficacy results obtained when TSP is spread with a spatula by medical technicians can be generalized to the expected method of application (i.e. spreading with fingertips by soldiers).
  - It is unclear whether a 60 minute wear time is necessary before TSP acquires barrier properties, and whether TSP-mediated barrier properties are retained past 60 minutes.
  - It is unclear whether under these experimental conditions TSP protects against penetration for longer than 15 minutes after exposure to permeants.

6.3 Heat Exchange Study

Protocol Number: Log No. TPMD95004-AP019-H018

Title: Effects of Topical Skin Protectant (TSP) on Heat Exchange in Humans

Study Dates: August and September, 1995
Study Location: Aberdeen Proving Ground, Maryland
Investigators: Lou A. Stephenson, Ph.D.

Co-Investigators: Margaret A. Kolka, Ph.D.
Catherine L.V. Gabaree, Ph.D.

NUMBER OF SUBJECTS: 10

AGES OF SUBJECTS: 18-31 years old

INCLUSION CRITERIA:

- Male or female subjects who are U.S. Army personnel, between 18 and 35 years old.
- To control for differences in core temperature induced by menstrual status, women volunteers were studied in the follicular phase of their menstrual cycles or during menses if they are taking oral contraceptives.
- Medically fit, as determined by medical history, physical examination (including dermatological examination), resting 12-lead EKG, and laboratory blood tests (CBC and differential, CHEM 26, serum pregnancy test for female volunteers).

- Subjects are free of medication which will affect thermoregulatory effector responses

EXCLUSION CRITERIA:

- Volunteers who smoke tobacco or who have a history of heat intolerance.
- Pregnant females.
- Volunteers with dermatologic irritations and history of contact sensitivity.
- Volunteers with a positive skin test response to TSP during screening prior to heat exchange study (see below).

STUDY OBJECTIVE/DESIGN:

To determine the impact of TSP applied to 21% BSA on thermoregulation in humans as they walk in an environment which has the biophysical characteristics to simulate temperature and water vapor pressure at the skin under chemical protective clothing. Specifically, the protocol was designed to answer the following two questions:

- Is core body temperature increased during exercise after application of TSP?
- Does TSP reduce tolerance time?

SOURCE OF STUDY MATERIALS:

The TSP (lot# 306 → 794, 307 ~ 794), provided by [redacted] were used in the study.

STUDY PLAN:

Objective/Rationale:

This was an open label single exposure unbalanced study of the potential for TSP to induce impairment of heat exchange in subjects.

Design:

This was a one study site open (unblinded) investigation. Patients served as their own controls in the study. The study was conducted in two stages: first subjects were tested for increases in core body temperature in an environment simulating MOPP 4 gear without TSP, and after 4 days, subjects were again tested with TSP applied to approximately 21% BSA.

PROTOCOL OVERVIEW:

Population, procedures

Eight men and two women were enrolled in the protocol. Sponsor analyzed results of the entire sample, and also the results of a subgroup of 8 subjects (absent S01 and S08). Sponsor's rationale for not including the results of the latter two subjects was that Subject 01's response during the TSP trial was different from his control trial, different from the other subjects, and consistent with sleep deprivation. Interviews with this subject revealed that he had been under considerable stress for weeks because of difficulties in his wife's first pregnancy. The data for Subject 08 was not included in the subgroup analysis because an unusual drop in his T_{es} (esophageal temperature) occurred after minute 55 during the TSP arm of the study, attributed to sinus drainage.

Reviewer's Comment:
The purpose of this study is to test whether the core temperature in subjects is increased when their skin is coated with TSP. The consequences of excluding from consideration the data from all "outliers", no matter how seemingly legitimate is the rationale, is to bias the analysis in favor of not detecting a difference in the treatment arms. A suitable means to minimize the impact of outliers on the data analysis would be to ensure the study is of sufficiently large size. The appropriate population for assessing increases in core body temperature would be all subjects tested (n=10).

Screening Phase
Volunteers were screened to ensure that they met eligibility criteria (specified above). To check for sensitization to TSP, subjects were exposed to 0.1 gram of TSP applied to a 2.25 cm diameter circle on the ventral forearm, distal to the antecubital space. Reactions were observed and recorded by the Medical Monitor at 1 hr, 24 hr, and 48 hr.

Study Procedure
Because TSP does not readily wash off skin and because complete removal from skin is not ensured from washing, testing for changes in body temperature after exposure in the test environment was always performed first with controls, then (after 4 days) with TSP applied. Subjects fasted overnight and arrived at the environmental chamber at the same time of day each morning without eating breakfast or drinking anything but water.

Subjects inserted the esophageal temperature probe themselves. For the TSP arm of the study, study personnel applied TSP on the neck, armpits, wrists, waist, inner thighs, and lower legs (boot tops). Skin thermocouples were applied to eight sites, and EKG was attached. During the heat exchange study, subjects' esophageal and skin temperatures were measured and recorded every 0.5 minutes, and heart rate was measured and recorded every 5 minutes.

Subjects entered the test environment (ambient temperature: $36 \pm 0.5^{\circ}C$, dew point temperature $27 \pm 1^{\circ}C$). This environment was designed to model the conditions of MOPP gear. After acclimating while seated for 14 minutes in the test environment, the subject stood for one minute as the treadmill was adjusted to a speed of 3.5 mph and a 3% grade. Walking commenced on this treadmill at 15 minutes of experimental time. Exercise was continued until volitional exhaustion or until the termination criteria for exercise (90% calculated maximal heart rate) or heat exposure (core temperature exceeding $39.5^{\circ}C$) were fulfilled.

Primary Efficacy Variable:
Body temperature was calculated from the esophageal and mean skin temperatures by the equation:

$$T_b = (0.9*T_{es}) + (0.1*T_{sk})$$

where T_b is body temperature, T_{es} is esophageal temperature, and T_{sk} is skin temperature (averaged across the eight measured sites).

Other analyzed variables included evaporative heat loss (a function of the change in dressed body weight during the study, the body surface area, and the latent heat of sweat vaporization), and the whole body sweating rate (calculated by dividing the differences between the pre- and post-experimental nude body weights by the tolerance time).

Clinical Endpoint: Completion of the two arms of the study.

Safety Results: Subjects were monitored for adverse events.

STATISTICAL ANALYSIS PLAN:
Two-way analysis of variance (time by treatment) with repeated measures was used to determine differences in heart rate, esophageal, and skin temperatures between control and TSP conditions. Sweating rate, tolerance time, evaporative heat loss, changes in esophageal temperature per minute of exercise time, and HR, T_{sk} ,T_{es} , and T_b at LCM (the last minute common to both treatment conditions) were compared using a paired t-test.

Based on sponsor's previous research, the sponsor claims that a sample size of 10 enables a power of 0.98 for esophageal temperature with an effect size of 0.1°C.

Study Results
Demographics

Demographics of 10 Evaluable Study Subjects		
Age	Mean	23.1 years
	Standard Deviation	4.8
	Range	(18,31)
Gender	Male	8 (80%)
	Female	2 (20%)
Race	Not available	
From Vol. 2.25, pg. 164		

Results
The following table provided by sponsor depicts the mean values and standard deviations of several statistics relevant to assessing heat tolerance at the last common minute (LCM) to control and TSP treatment during exercise. The p-values associated with these statistics were obtained from the paired t-test, under the null hypothesis that the parameters associated with these statistics were unchanged as a result of testing under control or TSP conditions.

Mean (± SD) tolerance time (TT), heart rate (HR), esophageal temperature (T_{es}), weighted skin temperature (T_{sk}), and body temperature (T_b) at LCM					
	Tolerance Time	HR at LCM (bpm)	T_{es} at LCM	T_{sk} at LCM	T_b at LCM
No. of subjects	10	10	9*	10	9*
Control	139 ± 32.50	158 ± 14	38.11 ± 0.50	36.11 ± 0.49	37.91 ± 0.47
TSP	132 ± 37.13	158 ± 15	38.28 ± 0.37	36.03 ± 0.38	38.05 ± 0.36
P-value	.29	1.00	.08	.50	.07
*T_{es} and T_b values for Subject No. 8 were not included because the subject experienced excessive nasal discharge during the TSP part of the study, which interfered with reliable reading of the T_{es} value					
From BZ submission, 11/24/99					

For both control and TSP arms of the study, T_{es} steadily increased as a function of exercise time. Change in T_{es} as a function of time was 0.012(± 0.003)°C-min^{-1} during the control arm and 0.014(± .003)°C-min^{-1} during the TSP arm. These calculations were based on the n=8 sample. The p-value for this comparison, calculated from two-way ANOVA, is 0.044. Sponsor notes in the study report that with this difference in rate of increase in the core temperature, "the difference between conditions would be 0.36°C after three hours and 0.48°C after four hours. Although in some instances this small difference could be physiologically significant, in service members wearing MOPP gear, this small difference in the rate of increase in esophageal temperature could be obscured by intra-individual metabolic variation."

Other measured statistics (skin temperature during exercise, heart rate, sweating rate, evaporative heat loss, tolerance time) did not differ significantly between the two study arms.

The sponsor notes (Vol. 2.25, pg. 147) that the TSP appears to "remain on the skin in the hot, humid ambient conditions of the tests for up to 188 minutes, however, the TSP appeared abraded in areas of continuous rubbing with clothing (e.g., waist, inner thighs). The application of TSP did not appear to inhibit sweating. Sweat appeared to emerge from the layer of TSP in areas where it was applied (e.g., neck, waist)."

Reviewer's Comment:
It appears from sponsor's analysis of the data that TSP application is not associated with an increase in core body temperature during exercise under conditions similar to what would be anticipated with use of MOPP gear.

It is unclear how reliably the results obtained in a test environment used to simulate MOPP gear can be extrapolated to conditions of actual MOPP gear use.

If TSP becomes abraded during wearing, and if sweat emerges from the layer of TSP in areas where it was applied, the possibility exists that any potential protection from CWA afforded by TSP degrades as users move about and sweat in their MOPP gear.

6.4 Mask Fitting Study
Protocol Number: A6786

Title: Quantitative Fit Factor Evaluation of Topical Skin Protectant (TSP) ICD 2289

Study Dates: August, 1995
Study Location: Aberdeen Proving Ground, Maryland
Investigator: Robert A. Weiss

NUMBER OF SUBJECTS: 43 enrolled (one subject (#19) withdrew following the control phase of this study)

AGES OF SUBJECTS: 18-40 years old. All subjects were male.

INCLUSION CRITERIA:
- Any individual who is in satisfactory health and judged fit to wear a respirator and protective clothing.

EXCLUSION CRITERIA:
- Subjects will be excluded if there is any evidence of the following conditions: claustrophobia, facial deformities that interfere with the seal of the mask, heart or circulatory disorders, skin rashes, lung or breathing disorders, head injury, or any other bodily injury which would prohibit wearing a mask or protective clothing and from performing the exercises.
- Subjects currently taking any medication or deemed unfit to perform light to moderate exercise.
- Subjects who are pregnant. (No female volunteers enrolled in this study).

STUDY OBJECTIVE/DESIGN:
To determine if the TSP alters the fit of the U.S. Army M40 chemical-biological protective mask.

STUDY PLAN:
Overview:
This is an open label single exposure study of the effect of TSP on the fit of the U.S. Army M40A1 chemical-biological protective mask. Test subjects were sized and fitted for their masks. The subject's faces were not washed prior to TSP application. Next, the subjects entered into an aerosol chamber. Within this chamber, a poly-dispersed aerosol challenge was generated by atomizing liquid corn oil. Simultaneously, air was sampled

from the mask. During this test, subjects performed a variety of exercises, (e.g. normal breathing, deep breathing, sighting a rifle). This test was repeated four times for each subject: two times with and two times without TSP applied to the face. The TSP (300 grams, Lot No. 305 — 794) was provided by [redacted]

Reviewer's Comment: In the field, facing imminent threat of CWA, individuals would presumably apply the TSP themselves. It is unclear that the results from the quantitative fit factor evaluation, where a technician has applied the TSP, can be extrapolated to circumstances in which the TSP is self-applied.

Primary Efficacy Variables:
The fit factor, defined as the ratio of the concentration of an external aerosol challenge relative to the aerosol concentration measured within the mask. (The larger the value, the greater the protection provided by the protective mask).

Clinical Endpoints: Completion of the four trials.

Safety: No adverse events were noted in this study.

Results:
This study showed a small but statistically insignificant improvement in the average protective performance of the M40 mask when TSP was applied to the face. The 90% confidence interval for the percentage of trials with TSP cream that passed at a fit factor of 10,000 was 94.9%-99.7%; the 90% confidence interval for the percentage of trials without TSP cream that passed at a fit factor of 10,000 was 93.2%-99.2%. Sponsor hypothesizes that TSP may fill in small crevices between mask and skin, thereby generating a better fit.

Reviewer's Comment: Sponsor noted that they were unable to enroll female volunteers for this study. According to the sponsor, there were logistical problems associated with requiring a serum pregnancy test as a prerequisite for study enrollment. Differences exist between men and women's facial anatomy and face skin. For example, men have more and thicker facial hair than women. Given these differences, it is unclear whether results obtained in male volunteers can be extrapolated to women.

7. Overview of Efficacy

In developing a clinical program to demonstrate the clinical efficacy of TSP for its proposed indication, sponsor was constrained because it was impossible to conduct clinical trials to assess whether TSP prevents CWA-associated morbidity or mortality in humans. Sponsor conducted animal efficacy experiments (i.e., testing TSP protection of animals from the effects of CWA/BWA), as well as human trials in which TSP was evaluated for its ability to protect volunteers from model permeants (urushiol and methyl nicotinate). Sponsor has convincingly demonstrated superior protection from permeants in numerous animal efficacy studies and in two human studies. The methyl nicotinate study has the added virtue of demonstrating that a significant barrier remains intact for at

least 80 minutes when subjects are exposed to a hot and humid environment—the type of environment subjects will experience when they don MOPP gear.

The difficulty in interpreting the efficacy data for the proposed indication lies in extrapolating results from animal efficacy studies and human studies with surrogate permeants to the scenario for which TSP was designed: armed forces personnel facing imminent CWA attack. How high a dose, topically applied, of CWA /BWA on a TSP-treated site could a human withstand? By how many minutes, or hours, does TSP delay penetration of CWA/BWA so that decontamination remains feasible? These questions cannot be directly answered.

While sponsor has accrued sufficient evidence of efficacy to support approval for this specific indication, other questions concerning TSP use that sponsor should be requested to address in post-approval studies include:

- How effective is the TSP barrier if volunteers themselves, rather than trained medical personnel, apply and spread the TSP?
- How effective is the barrier if fingertips, rather than a steel spatula, are used to spread the TSP?
- How effective is the barrier if less than one hour elapses between TSP application and challenge with a permeant?
- How necessary is cleansing the skin with isopropyl alcohol and letting it air dry for effective application of TSP?
- Is the M291 Decontamination Kit as effective as Cetaphil®/water for decontamination, when used in conjunction with TSP?
- Does DEET abrogate TSP protection of human skin to a similar degree that it abrogates protection of animal skin?

8. Overview of Safety

That perfluoroalkylpolyether is a common ingredient in cosmetics, and that polytetrafluoroethylene has many uses as a part of indwelling medical devices, argues that TSP components have a substantial record of safe human use. There are few safety concerns pertaining to systemic bioavailability of topically applied TSP because sponsor has demonstrated that the product does not penetrate beyond several cell layers into the stratum corneum (see Section 5 of this review and Biopharmaceutics Review). Results of topical safety studies were consistent with TSP being biologically inert. No treatment-emergent adverse events were described for any participants in the clinical trials.

The possibility exists that if PTFE contaminates a cigarette and an individual subsequently smokes that cigarette, untoward health effects may ensue. Such a scenario is not unlikely: the medical reviewer has calculated that if as little as .001% of the recommended dose of TSP inadvertently contaminates a cigarette, an individual who smokes that cigarette may develop polymer fume fever. Given the substantivity of TSP, it would not be unreasonable to expect this much PTFE to remain on the hands of a subject after it has been spread onto the target surfaces. This makes a consideration of the consequences of polymer fume fever to the health of subjects a topic worthy of

consideration in assessing safety issues pertaining to this NDA. Accordingly, the sponsor prepared a critical review of the literature about polymer fume fever (Chatfield and Darwell, "Polymer-Fume Fever: A Review", Vol. 2.26, pp. 002-017). This review is the information source for the following discussion of polymer-fume fever, except where other references are specifically cited.

Polymer-fume fever (PFF) has been described among industrial workers exposed to pyrolysis fumes of polytetrafluorethylenes (PTFE). (TSP is a 50:50 mixture of PTFE particles dispersed in perfluoropolyethers (PFPE)). There are two settings in which industrial workers were exposed: either directly, through inhalation of pyrolyzed PTFE during various industrial processes (e.g., tack-welding drawer glides with Teflon components), or indirectly, through the smoking of PTFE-contaminated cigarettes. In experimental studies, smoking a cigarette contaminated with a single particle (as little as 400 micrograms) of PTFE, or smoking 10 cigarettes (doped with 50 micrograms of PTFE each) in a 4 hour period, was sufficient to induce PFF. An indication of how little PTFE is required to induce PFF are that case reports describe a woman who developed PFF by smoking a cigarette while handling her son's PTFE-contaminated clothing. While a general lack of hand-washing before smoking has been described among industrial workers who contract PFF, in one industrial setting, workers developed PFF despite efficient air circulation in the plant, dissemination of instructions to workers to wash their hands prior to smoking, and the prohibition of smoking and the presence of cigarettes in the workplace. It was presumed that PTFE residue present in workers' beard, hair, and work clothing accounted for the attacks among workers who observed these precautions. Since TSP, which is PTFE in a viscous suspension, would presumably be more difficult to wash off skin surfaces than free PTFE particles, it may provide a higher hazard of contaminating cigarettes than would free PTFE. It is noteworthy that most case reports state that the workers characterize the contaminated cigarettes they smoked as "tasting bad", or making them nauseated.

PTFE pyrolysis fumes are composed of a complex mixture of minute volatilized particles along with several toxic gaseous compounds (e.g., hydrogen fluoride, carbonyl fluoride, and aliphatic and cyclic saturated and unsaturated fluorocarbon compounds). All of these compounds are primary pulmonary irritants. The complexity of this mixture has thus far prevented researchers from definitively identifying which component(s) trigger PFF, or the mechanism by which the pulmonary and systemic changes are triggered. Lee and Seidel ("Pulmonary Response to Perfluoropolymer Fume and Particles Generated under Various Exposure Conditions", Fund. and Appl. Toxicol., 1991; 17: 254-269) reported the results of animal studies in which rats tolerated without pathological changes exposure to pyrolysis fumes that had been filtered to remove particles, but developed pulmonary edema and hemorrhage when exposed to unfiltered particles. Animals that survived this challenge developed focal emphysema and interstitial fibrosis. Electron microscopic analysis detected damage to Type I pneumocytes, which can result in alveolar edema. These results suggest that minute volatilized particles of PTFE particles may be intrinsically pathogenic, or may act as a carrier of adsorbed toxins.

Particles collected from PTFE pyrolysis fumes and injected intravenously into rabbits induced fever and leukocytosis, while washed particles collected in like manner failed to do so: the interpretation of this experiment was that a water soluble, volatile component of PTFE fumes adsorbed to the surface of PTFE particles renders the particles capable of interacting with blood leukocytes and triggering their degranulation and release of pyrogenic compounds (e.g., TNF-α and il-1). It is reasonable to hypothesize that the systemic release of these bioactive molecules are the cause for the systemic symptoms (see below) described by patients with PFF.

The medical literature contains case reports or observational series of 121 subjects who developed PFF, 61 of whom developed PFF as a consequence of smoking PTFE-contaminated cigarettes. The most common symptoms of PFF include:

- Chest discomfort, especially upon deep inhalation
- Dry, irritating cough, which worsens as the chest discomfort worsens
- (After 2 to 3 hours) Malaise, fatigue, headache, nausea, weakness, aching limbs, fever/chills, increased respiratory and heart rate.
- (More rarely) Numbness, tingling of extremities, sore throat, sputum production, profuse sweating, and lightheadedness.

The following table from one such observational series (Silver, MJ and Young, DK, Acute noncardiogenic pulmonary edema due to polymer fume fever, Cleve. Clin. J. Med. 1993; 60: 4769-482, who cite Harris, DK, Polymer fume fever, Lancet 1951; 2: 1001-1011) describes the relative prevalences of these signs and symptoms in a set of patients diagnosed with polymer fume fever:

	Number of patients	Percentage
Symptoms		
Myalgia	62/65	95
Chest Tightness	101/108	94
Chills	94/109	86
Dyspnea	93/109	85
Malaise	40/47	85
Cough	90/111	81
Headache	27/40	68
Sore Throat	11/42	26
Signs		
Sputum Production	1/41	2
Tachypnea	5/6	83
Fever	96/117	82
Crackles	4/7	57
Laboratory Findings		
Leukocytosis	6/8	75

Five case reports describe PFF-associated acute non-cardiogencic pulmonary edema confirmed by chest X-ray, associated with symptoms of respiratory distress, chest pain, or recurrent cough. These symptoms subsiding within 72 hours to a week after onset.

Two case reports describe longer-lasting PFF-associated sequelae. Brubaker relates the case of a 24 year old male who reportedly smoked only one PTFE-contaminated cigarette. Three weeks after exposure, he was still complaining of chest pain and recurrent cough. Pulmonary function tests performed at that time revealed he had reversible pulmonary obstruction with a reduction in diffusing capacity. Examination two months after the attack revealed the patient to be asymptomatic, without evidence of airway obstruction, but diffusing capacity remained below normal expected levels. Williams et al. (Polymer-Fume Fever: Not So Benign, J. Occup. Med. 16: 519-522) describe the case of a 50 year old woman who suffered more than 40 bouts of PFF in a 10-month period before the etiology of her illness was recognized. More than three years after her diagnosis, the patient returned to her physician with complaints of a constellation of symptoms, including persistent fatigue, dyspnea on exertion, tightness of chest after exposure to dust, photosensitivity, and an erythematous to papulo-vesicular eruption. Based on pulmonary function tests, the patient was diagnosed with alveolar-capillary block syndrome. The patient subsequently died of unrelated causes (berry aneurysm/ subarachnoid hemorrhage). An autopsy revealed significant interstitial pulmonary fibrosis. The authors speculated that the likely etiology of the fibrosis was that the fumes had a direct fibrogenic effect on the pulmonary interstitium, or that it may result from organization of intra alveolar exudates such as protein-rich edema fluid. While this patient's illness may have been caused by chronic inhalation of PTFE pyrolysis products (and her autopsy findings parallel those of the animals who developed interstitial fibrosis after exposure to PTFE fumes), the possible diagnosis of idiopathic interstitial fibrosis cannot be excluded. Based upon these findings, the authors of the case report concluded: "diagnosed cases of polymer fume fever, even in the absence of clinical or radiological pulmonary edema, should no longer be regarded as suffering from a transitory and benign condition, particularly if there is a history of previous attacks."

The diagnosis of polymer fume fever is usually made on the basis of historical and clinical data alone. While urinary fluoride is an excellent index of time-weighted average fluoride exposure in industrial situations, random urine fluoride concentrations may not detect toxicologically significant acute exposures to PTFE pyrolysis products unless specimen timing is optimal. Studies have detected elevated urinary fluoride levels in exposed industrial workers and laboratory animals, but these studies involved subacute or chronic exposures (Shusterman, DJ, Polymer Fume Fever and Other Fluorocarbon Pyrolysis-Related Syndromes, Occupational Medicine, 1993, 8: 519-531).

It is reasonable to hypothesize that there is a continuum of disease severity, depending upon the degree and chronicity of exposure. With low exposure, mild self-limiting symptoms appear, perhaps associated with clinically and radiologically undetectable pulmonary edema. With higher exposure, symptoms are somewhat more severe and longer lasting, and pulmonary edema is both radiologically detectable and clinically diagnosed (i.e., rales/crackles). Chronic exposure to PTFE fumes may result in

pulmonary interstitial fibrosis, abnormal pulmonary diffusing capacity, and alveolar-capillary block syndrome. Based upon the higher frequency of reports describing transient mild symptoms compared to reports describing chronic pulmonary fibrosis, it appears that patients who suffer PFF are more likely to have mild, self-limited cases with no long term sequelae. There is one case report of death associated with acute polymer fume fever, in a factory worker suffering heavy exposure to PTFE in an industrial setting. There are no case reports of death following the smoking of contaminated cigarettes.

There is no specific therapy for polymer fume fever. Shusterman et al. have the following recommendations: (1) supportive treatment, including antipyretics and hydration, for mild cases; (2) inhaled bronchodilators if wheezing or other obstructive symptoms are apparent; (3) patients with productive cough or bronchospasm may also be candidates for inhaled steroids, since untreated chemical bronchitis has been postulated to induce nonspecific bronchial hyperresponsiveness; and (4) patients with chemical pneumonitis may require oxygen by nasal cannula or mask. Williams et al. recommended administering short term steroid treatment to prevent organization of protein rich edema fluid.

Significant/Potentially Significant Events
No significant or potentially significant events attributable to TSP exposure emerged in the clinical studies described in this review.

Overdosage Exposure
No information is presented.

Laboratory Findings, Vital Signs, ECGs
No significant changes in laboratory findings, vital signs, or ECGs attributable to TSP exposure emerged in the clinical studies described in this review.

Drug-Demographic Interactions
The vast majority of patients enrolled in the safety and efficacy studies were white or light-skinned. This was a practical necessity, as prevention or reduction of permeant-induced skin reddening was the criteria by which TSP barrier property was assayed. There is no reason to expect a difference in the quality of the barrier for patients of different skin types.

Because this product is intended for individuals who are members of the armed forces potentially at risk for exposure to CWA/BWA, there would be no regulatory utility for studying TSP barrier or safety in geriatric or pediatric populations.

Drug-Disease Interactions
Because all the subjects enrolled in this study were normal healthy volunteers, no information relating to drug-disease interactions are available.

Drug-Drug Interactions
No information was presented to assess drug-drug interactions.

Withdrawal Phenomena/Abuse Potential
No information was presented. The potential for abuse of TSP seems remote.

Human Reproduction Data
No information was presented to assess drug-drug interactions.

Safety Conclusions
The most significant safety risk associated with use of this product would be if those who prescribe it or use it operate under the mistaken impression that TSP is sure to completely protect against cutaneous CWA/BWA exposure. Based on the non-clinical and clinical studies submitted to this NDA, it is not possible to quantify the risk reduction from CWA/BWA exposure associated with TSP use in conjunction with Mission Oriented Protective Posture (MOPP) Gear. Because not all human subjects were completely protected by TSP from reacting to surrogate permeants (urushiol, methyl nicotinate) and because not all animals were completely protected from percutaneous exposure to CWA/BWA, a conclusion that TSP may be less than 100% effective at preventing percutaneous penetration of CWA/BWA would not be inconsistent with the results observed in these clinical studies.

Under the narrowly constrained conditions of use in the human clinical trials, which may not necessarily match the conditions of use by subjects under battlefield or training conditions, TSP does not appear to have a significant amount of risk associated with its use. The amount of systemic exposure following application of TSP to intact skin was below the level of detection, and the TSP does not appear to have penetrated through the stratum corneum of intact skin. No local cutaneous adverse events were noted in the human studies.

Sponsor has not conducted studies which would permit an estimation of the health risk to subjects who apply TSP to their skin and who subsequently smoke cigarettes. It would be necessary and appropriate to include in any final package labeling language that strongly advises patients not to smoke tobacco products after TSP has been applied to their skin surface, and to wash their hands thoroughly to remove all visible traces of TSP prior to handling tobacco products. However, it is to be expected that those soldiers who have the habit of smoking cigarettes may find it difficult to resist the temptation to smoke, despite the most stringent language warning them of the potential dangers. It may not be feasible under every battlefield scenario for soldiers to wash their hands thoroughly prior to handling their tobacco products.

9. Recommendations

Approval

The sponsor has not sufficiently characterized the potential for risk from use of TSP for it to be approved except under narrowly circumscribed circumstances of use in which the potential benefit of use is great (i.e., for use in conjunction with standard CWA protective measures, under circumstances in which the possibility of imminent exposure to CWA/BWA in the battlefield is expected). Thus, approval for TSP use in a non-military

setting is not justified, principally because of the unknown risks from individuals applying TSP to themselves and then smoking cigarettes inadvertently contaminated with TSP. Approval for TSP use in a training setting by military personnel is not justified for the same reason. It is recommended that this application be approved, provided that Phase 4 studies (as outlined below) are undertaken.

Phase 4 studies
To permit more complete assessment of the barrier property and safety profile of TSP, the following Phase 4 studies are suggested:

Sponsor should perform a study to characterize whether there is the potential for an interaction between TSP and the battledress uniform/overgarment that would result in the compromise of the barrier property of the standard CWA/BWA protective measures.

Clinical information exists that relates the degree of severity of PFF to the dose of PTFE particulates contaminating a cigarette. From this information, it would be possible to extrapolate the expected degree of severity of PFF in TSP users, if the amount of TSP that might be found on a contaminated cigarette were known. To estimate this, two pieces of information would be needed: (1) an estimate of the amount of residual TSP remaining on subject's hands following TSP application, and (2) an estimate of the extent to which TSP transfers to cigarettes when cigarettes are handled by someone whose hands contain TSP residue. Accordingly, Sponsor should perform a study to quantify the amount of residual TSP remaining on the hands of subjects who apply TSP to themselves and then attempt to remove the TSP from their hands, with or without washing. As a component of this study, sponsor should ascertain whether it is possible for a person who has applied TSP to him- or herself and then has attempted to remove the TSP from his or her hands (with or without washing) to contaminate a cigarette by handling it. As a control arm in this study, it may be useful to determine the extent to which handled cigarettes can be contaminated by subjects who handle PTFE particulate powder and then attempt to remove the PTFE particulate powder residue (with or without washing). The rationale for such a control arm would be that if the extent of PTFE contamination in the PTFE particulate arm is greater than the extent of PTFE contamination in the TSP arm, it would be reasonable to interpolate that the public health risk of PFF in subjects who use TSP is no greater than that of industrial workers involved in PTFE

No labeling comprehension study or actual use study were submitted as part of the NDA. Sponsor should perform an actual use study to determine whether subjects can apply to themselves a thin coat of TSP that reduces or prevents the penetration of a dermal permeant. Sponsor should characterize how much time can elapse between TSP application and the development of a cutaneous barrier. Sponsor should characterize how long the barrier remains on the skin. Sponsor should characterize the consequences of not cleaning the skin with isopropyl alcohol prior to TSP application on the barrier properties of TSP. Sponsor should characterize potential interactions between the M291 Skin Decontamination Kit and TSP.

/S/ 1/07/00

Martin M. Okun, M.D., Ph.D.
Medical Reviewer

cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin
HFD-540/Dermatology Team Leader/Walker
HFD-540/Medical Reviewer/Okun
HFD-725/Biostatistics Team Leader/Al-Osh
HFD-725/Biostatistician/Friedlin
HFD-880/Biopharm/Bashaw
HFD-540/Pharm/Reid
HFD-540/Chemistry/Timmer
HFD-540/Project Manager/Cross

/S/ 1/10/00

/S/ 1/19/00

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JAN 18 2000

Medical Officer Review of NDA 21-084: Addendum

Date: January 19, 2000

As per FDA Form 3454, submitted September 24, 1999, Sponsor has certified that no financial arrangements with investigator have been made where outcome affects compensation, and that investigator has no proprietary, significant equity interest or any significant payments in the clinical studies performed in support of this NDA. The certified studies include "An Assessment of the Ability of the Topical Skin Protectant (TSP) to Protect Against Contact Dermatitis to Rhus Antigen", in which the principal investigator was D. Vidmar, and "The Protective Efficacy of the Topical Skin Protectant ("TSP") Against Methyl Nicotinate Under Sweating Conditions", in which the principal investigator was W. Cunningham.

/S/ 1/19/00

Martin M. Okun, M.D., Ph.D.
Medical Reviewer

cc:
Archival NDA TSP - USMRMC
HFD-540
HFD-540/Division Director/Wilkin
HFD-540/Dermatology Team Leader/Walker /S/ 1/19/00
HFD-540/Medical Reviewer/Okun
HFD-725/Biostatistics Team Leader/Al-Osh /S/ 1/20/00
HFD-725/Biostatistician/Friedlin
HFD-880/Biopharm/Bashaw
HFD-540/Pharm/Reid
HFD-540/Chemistry/Timmer
HFD-540/Project Manager/Cross

APPEARS THIS WAY
ON ORIGINAL

JAN 2 9 2000

Medical Officer Review of NDA 21-084: Addendum

Date: January 28, 2000

Subject: Study Design of the Clinical Study entitled "The Protective Efficacy of the Topical Skin Protectant ("TSP") Against Methyl Nicotinate Under Sweating Conditions"

On page 32 of the Medical Review of this NDA, the following statement in Reviewer's Comments pertaining to the study design of the above-mentioned study appears:

"As one potential source of bias, during laser doppler readings, it is necessary for all the patient's test sites to be equidistant from the laser source. Sites further from the laser would be read as having lower flux, and sites closer to the laser would give readings of higher flux. Theoretically, inadvertent misalignment of the laser could generate anomalous recordings."

On further review of the Sponsor's submission, the Medical Reviewer concluded that the above comment should be retracted. The basis for this retraction is that the Sponsor notes in Vol. 2.39, pg. 035 that "the distance between the mirror and the skin surface is not critical" for operation of the Laser Doppler Scanner.

/S/ 1/28/00

Martin M. Okun, M.D., Ph.D.
Medical Reviewer

cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin /S/ 1/28/00
HFD-540/Dermatology Team Leader/Walker
HFD-540/Medical Reviewer/Okun
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HFD-725/Biostatistician/Friedlin
HFD-880/Biopharm/Bashaw
HFD-540/Pharm/Reid
HFD-540/Chemistry/Timmer
HFD-540/Project Manager/Cross

APPEARS THIS WAY
ON ORIGINAL